

## Does Ticagrelor better than Clopidogrel in Peripheral Artery Disease?

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**Abbreviations** CAPRIE: Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events; EUCLID: Examining Use of Ticagrelor in Peripheral Artery Disease; PAD: Peripheral Artery Disease; MI: Myocardial Infarction; PEGASUS-TIMI 54: Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54; TIMI: Thrombolysis In Myocardial Infarction.

### Editorial

Peripheral artery disease (PAD) is a clinical manifestation of systemic atherosclerosis localized in lower limb arteries. It's associated with a high risk of adverse cardiovascular and limb events even in the absence of a history of clinical cardiac or cerebral ischemic events [1,2].

### Guidelines for antiplatelet therapy in PAD are limited due to a lack of specific trials

In the subgroup of patients with PAD from the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events), clopidogrel reduced significantly the incidence of ischemic events compared to aspirin [3]. In the subgroup of patients with a history of myocardial infarction (MI) and concomitant PAD from the PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54), ticagrelor a potent, direct-acting and reversible P2Y<sub>12</sub> adenosine diphosphate receptor blocker reduced the absolute risk of cardiovascular events [4]. In order to develop evidence for antiplatelet therapy in PAD, the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial was performed to verify if ticagrelor in monotherapy can reduce significantly cardiovascular events compared to clopidogrel. The multicenter double-blind EUCLID trial [5], randomized 13,855 patients with PAD (811 centers, 28 countries) ticagrelor (n=6930) 90 mg<sup>2</sup>/day or clopidogrel (n=6955) 75 mg/day. They had symptomatic PAD with either an ankle-brachial (ABI) ≤ 80 at the time of screening or who had undergone revascularization of the lower limbs more than 30 days previously. Patients under double antiplatelet therapy, under aspirin, under anticoagulant treatment and homozygous for the cytochrome P450C219 were excluded. The primary endpoint was composite: cardiovascular death, infarction (MI), ischemic stroke. The secondary endpoint was the primary endpoint plus acute limb ischemia. The primary safety end point was

major bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria. The patient's characteristics were as follow: an average age of 66 years, 72% were men, 30% were smokers and 38% had diabetes. ABI was, on average, 0.71 for all patients and 76.6% suffered from claudication. After 14 months of treatment and 30 months of follow-up, there were no significant difference in the primary efficacy composite end point who was observed in 751 of 6930 patients (10.8%) in the ticagrelor group and in 740 of 6955 (10.6%) in the clopidogrel group (HR=1.02, 95% CI: 0.92-1.13, p=0.65). However a significant difference was observed for ischemic stroke: 1.9% with ticagrelor versus 2.4% with clopidogrel (HR=0.78, 95% CI: 0.62 to 0.98, p=0.03).

Concerning secondary efficacy end point and safety data, acute ischemia of the limbs and severe bleeding were observed in the two groups in a similar way, respectively 1.7% and 1.6%. Important point to report, ticagrelor was discontinued more frequently than clopidogrel (30.1% versus 25.9% respectively, HR=1.21, 95% CI: 1.14 -1.29; P<0.001) mainly due to side effects (dyspnoea, minor bleeding). So, what EUCLID shows are that in patients with PAD, prevention is similar with clopidogrel and ticagrelor for many reasons. First of all, in our study clopidogrel was a potent and effective comparator. Secondly, the investigators excluded patients who were homozygous for loss-of-function alleles to clopidogrel. And finally patients with concomitant clinical coronary artery disease were minority. In conclusion, ticagrelor doesn't reduce significantly the rate of cardiovascular events compared to clopidogrel in patients with symptomatic PAD. The rates of major bleeding were similar. However, due to side effects (dyspnea, minor bleeding), ticagrelor was discontinued more frequently than clopidogrel.

### References

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